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Background: Ustekinumab, a monoclonal antibody of interleukin-12 and interleukin-23, was approved for the treatment of moderate to severe Crohn’s disease (CD) in 2016. Ustekinumab is approved in CD for a weight-based IV induction dose followed by every 8 weeks of subcutaneous dosing. Response rates by 6 weeks range from 34% (anti-TNF failures) to 56% in bio-naive patients. The remainder includes patients who partially respond (PR) or do not respond (NR). Response by week 16 is 55% (anti-TNF failures) and 73% in bio-naive patients suggestive of a delayed response. Experience with anti-TNF drugs demonstrates that a subset of patients respond to dose escalation, which prompts the notion of a potential delayed response phenomenon with Ustekinumab.

Aim: Determine the efficacy of dose escalation from standard Q8 dosing to Q4 dosing of Ustekinumab in CD patients, who had PR or NR to standard Q8 dosing.

Methods: A Retrospective observation study of 143 adult patients with CD, on Ustekinumab standard Q8 dosing over a 2 year and 9-month period was conducted. Data was extracted pertaining to demographics, disease, and treatment-related variables (biomarkers, steroid use, interval surgery, ER visits). Patients were further subcategorized as responders, partial responders (PR), and non-responders (NR), based on changes in fecal calprotectin, albumin, CRP, and Physician Global Assessment Disease Severity (1=mild, 2=moderate, 3=severe). Q8 non-responders (NR) and partial responders (PR) were dose-escalated to Q4, and outcome variables were collected. Biomarkers, steroid utilization, interval surgery, and ER visits, and PGA were compared in Q8 partial responder (PR) and non-responders (NR) from the date of starting Ustekinumab on Q8 dosing to the date of escalation to Q4 dosing, versus the date of escalation Q4 dosing to the end of patient follow up.

Results: 30% (n=8) of patients were Q8NR, and 70% (n=19) were Q8PR. In the PR group, biomarkers decreased by up to 21% when these patients were switched to Q4 dosing. 100% of patients saw clinical improvement or remained at mild disease while on Q4 dosing. In both groups, 50% of patients taking steroids on Q8 dosing were no longer taking steroids or were at a reduced dose at the end of Q4 dosing follow-up. 40% of patients on immunomodulators on Q8 dosing were no longer taking immunomodulators at the end of Q4 dosing follow-up.

Conclusions:
1) - Dose escalation of Ustekinumab to every 4 weeks improves CD response rates in patients who appear to be failing or partially responding to standard dose Ustekinumab.
2) - Dose escalation of Ustekinumab should be considered in all CD patients failing to achieve remission with standard dosing.
Uncontrolled Therapeutic Observations in Humans Using Biologic or Non-Biologic Agents

ustekinumab is not yet FDA approved for UC, for patients who have exhausted other treatment options its use is considered "off-label". Patient demographics, disease characteristics and prior treatment history were recorded. The primary outcome was clinical remission at 12 months after initiation of ustekinumab. Secondary outcomes were clinical response and remission at 3 months, and endoscopic response, corticosteroid-free remission, and deep remission (combined clinical and endoscopic remission) at 12 months (all outcomes defined in Figure 1).

Results: 19 pts received ustekinumab for moderate-to-severe UC. They were 47.4% male with a mean age of 42.7 ± 17.0 years. Mean total Mayo score was 7.6 ± 1.2 and 47.4% of pts had disease limited to the left colon. 18/19 pts received a weight-based IV induction dose (520 mg, 390 mg or 260 mg for > 85 kg, >55 to 85 kg or ≤55 kg respectively) and 1/19 received 90mg subcutaneous injection as induction. All pts received 90mg subcutaneous injections every 8 weeks initially for maintenance, and 9/19 eventually needed dose escalation to every 4 weeks. All pts had prior exposure to a TNF antagonist, 26.3% had exposure to two or more TNF antagonists, 89.5% had prior failure of vedolizumab and 10.5% had prior failure of tofacitinib (Table 1). At 12 months, 38.5% had a clinical response, 30.8% were in clinical remission, 38.5% had an endoscopic response, and 30.8% were in deep remission (Figure 1). Two infectious adverse events (shigellosis, Escherichia coli enterocolitis) were reported in follow-up.

Conclusions: Ustekinumab is effective in patients with UC. The efficacy of ustekinumab in the UNIFI trial translated to our real-world population, despite higher rates of prior biologic failure with TNF antagonists and vedolizumab in our cohort. Further studies of large, real-world cohorts are needed to assess the long-term effectiveness and safety of ustekinumab in UC.

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REAL-WORLD EXPERIENCE WITH TOFACITINIB FOR THE MANAGEMENT OF CROHN’S COLITIS
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Background: Treatment options in Crohn’s disease (CD) are limited. Tofacitinib, a Janus Kinase 1–3 inhibitor, is not currently approved for use in CD, however, its effect on biochemical markers suggests that tofacitinib does impact disease activity in CD.

Methods: We evaluated 5 adult patients with moderate-to-severely active Crohn’s colitis who were started on tofacitinib therapy after failing ≥2 biologic agents. Pre- and post-tofacitinib treatment characteristics including clinical, endoscopic and biochemical disease activity, presence of extra-intestinal manifestations, and potential adverse effects were recorded (figure 1). Endpoints evaluated were clinical remission (defined as Harvey Bradshaw index (HBI) ≤4) and response (>50% reduction in HBI); endoscopic remission (simple endoscopic score (SES)-CD≤3) and response (>50% reduction in SES-CD); and biochemical remission (focal calprotectin (FC)≤50 μg/g).

Results: Post-tofacitinib, patients were followed for a median period of 18 weeks (range 8–34 weeks). Four of the 5 (80%) patients achieved clinical remission, 4/5 (80%) achieved clinical response. All patients that underwent a follow-up endoscopy (n=3) achieved endoscopic response and 2/3 (67%) achieved endoscopic remission (figure 2). Three of the 4 patients with a follow-up FC (75%) achieved biochemical remission. Of the 4 patients on baseline corticosteroids, 3 (75%) were corticosteroid-free by week 18. Four of the 5 (80%) patients exhibited improvement in CD-related arthropathy. No significant treatment-emergent adverse events were observed.

Conclusions: In this case series, use of tofacitinib was safe and effective in the treatment of refractory Crohn’s colitis and CD-related arthropathy. Further investigation of tofacitinib in CD, particularly involving the colon, is warranted.

Table. Pre- and post-tofacitinib treatment characteristics of the 5 study patients

| Pre-treatment Characteristic | N | %
|-------------------------------|---|---
| Age (years)                  | 20 | 40.0
| Gender (M:F)                 | 2:3 | 40.0
| Prior TNF antagonist         | 4:1 | 80.0
| Prior tofacitinib treatment  | 4:1 | 80.0
| Fecal calprotectin (μg/g)    | 875 | 175.0
| Clinical response (HBI ≤4)   | 5/5 | 100.0
| Clinical remission (HBI ≤4)  | 5/5 | 100.0
| Endoscopic response (SES-CD ≤3) | 5/5 | 100.0
| Endoscopic remission (SES-CD ≤3) | 2/3 | 66.6
| Biochemical remission (FC ≤50 μg/g) | 3/4 | 75.0
| Corticosteroid-free by week 18 | 3/4 | 75.0
| Improvement in CD-related arthropathy | 4/5 | 80.0

*All values reported as mean ± SD or as n (%).
**Pre- and post-tofacitinib treatment characteristics of the 5 study patients.

Table 1 – Patient Demographics, Disease Characteristics and Treatment History*